REMARKS/ARGUMENTS

Claims 10-14, 17, 19, 20, and 33-78 are active in this application. Support for the amendments to Claims 62, 66, 70, 64, 68, 72 and Claims 74-78 is found on page 3 of this application. In addition, the claims presented have been renumbered according to the Examiner's statement on page 2 of the Official Action. No new matter is added.

Applicants thank the Examiner for indicating that Claims 10-14, 17, 19, 20 and 33-61 are allowed. In light of the following remarks and the attached executed Declarations reconsideration of the rejection of Claims 63-73 is requested.

Applicants also thank the Examiner for the courtesy of discussing this case with Applicants' undersigned representative on March 9, 2004. During this discussion the Examiner suggested amending the scope of the method claims and consistent with that discussion, the claims have been amended to recite inflammatory arthritis, which is described and enabled by the application.

Before getting into the substance of the rejection, Applicants request that the Examiner reconsider the finality of the outstanding Office Action. As a basis for issuing a final Office Action following the request for continued examination, the Examiner states "all claims are drawn to the same invention claimed in the application prior to entry of the submission under 37 C.F.R. § 1.114 and could have been finally rejected on the grounds of art of record in the next Office Action if they had been entered in the application prior to entry under 37 C.F.R. § 1.114." (Page 16 of the Official Action). However, the request for continued examination was filed because the Examiner stated in the Advisory Action of August 19, 2003 (paper No. 29) that the proposed amendments would not be entered because "they raise new issues that would require further consideration and/or search" and particularly "amended and newly added claims raise new issues with respect to the scope of

the claims since the claims are now limited to specific compounds administered *in vivo* to treat an inflammatory condition arthritis or contacted antagonizing or agonizing a C5a receptor. However, such *in vivo* administration to treat the above situations were not dealt with previously, and as such would require further consideration and search." Therefore, the finality of the Office Action seems to run contrary to the opinion of the Examiner in the Advisory Action. In other words, the RCE was filed because the Examiner would not enter the amendments and then issued a first action final rejection. Not only is this unfair to the Applicants but it is deemed to be improper and therefore it is respectfully requested that the finality of the rejection be withdrawn.

Turning to the rejection of Claims 62-73 under 35 U.S.C. § 112, first paragraph, this rejection is respectfully traversed for the following reasons.

As stated previously, Claims 62-63 are enabled because the Applicants have provided *in vivo* data using well-accepted models for assessing anti-inflammatory and anti-arthritis effects. The data presented in the application are shown in Examples 7 and 8 on pages 45-46. In particular, Example 7 demonstrates the inhibition of C5a induced neutropenia *in vivo* using one of the inventive compounds. In addition on page 46, the cyclic antagonists in Table 5 were determined to be active anti-inflammatory agents in suppressing the onset of either carrageenan-induced paw oedema or adjuvant-induced polyarthritis.

On page 46, the Applicants have also shown in the carrageenan paw oedema assay "that even weak C5a antagonists significantly inhibits development of the oedema after 180 and 270 minutes." Moreover, in a recent publication, which is of record, data are presented which demonstrate the efficacy of compound No. 12 in an antigen-induced arthritis model in the rat.

Notwithstanding these data, the Examiner has maintained the enablement rejection alleging that the specification "does not reasonably provide enablement for a method of

treating an inflammatory condition or a method of treating arthritis by administering the above compounds thereof as claimed in Claims 62-73." (Page 3 of the Official Action). Furthermore, the Examiner has stated that "the quantity of experimentation necessary states the phrases "treating inflammatory condition" and "treating arthritis" are not justified by the limited exemplary disclosure of suppressing the onset of either carrageenan-induced paw oedema or adjuvant-induced polyarthritis as disclosed in Figures 8-10 in Examples 7 and 8 because the above phrases encompass treating any kind of inflammation (unspecified inflammation caused by unspecified agent) as well as any kind of arthritis (undefined arthritis) using pharmaceutical formulations..." (page 7 of the Official Action). Applicants respectfully disagree.

First, as noted above, the claims have been amended to recite "inflammatory arthritis" and Claims 74-78 further define the inflammatory arthritis as "rheumatoid arthritis." Second, as discussed above, the data presented in the originally filed specification clearly enables these methods. However, as further support for the claimed methods, Applicants submit herewith two Declarations from Dr. Steven Taylor and Dr. Vivian Santer attesting to the enablement of the method claims in the current application.

Dr. Taylor has an extensive history and knowledge in inflammation research as shown by his statement attached to the Declaration as Appendix A and his *curriculum vitae* attached as Exhibit SMT-1.

Applicants direct the Examiner's attention to paragraph 5 on page 2 of Dr. Taylor's Declaration where he states:

> I consider that in fact the model systems described in the specification are very well accepted as being generally predicative of anti-inflammatory efficacy, not only in the treatment of rheumatoid arthritis but in other inflammatory conditions. Moreover, I consider that efficacy and the treatment of rheumatoid arthritis is regarded as being reasonably predicative of efficacy and other inflammatory arthritides.

Furthermore, the Examiner's attention is drawn to paragraph 7 of Dr. Taylor's Declaration (found on page 2) in which he describes the performance of additional assays both *in vitro* and in the rat carrageenan paw oedema model and rat adjuvant arthritis model described in the specification demonstrating that compounds of the invention have anti-inflammatory and anti-arthritic activity. The results are presented in a published manuscript and are attached to Dr. Taylor's Declaration as Exhibit SMT-2.

With respect to the predicative value of the rat paw oedema assay the Examiner's attention is directed to paragraph 11 of Dr. Taylor's Declaration (found on page 3) wherein he states

> I emphasize that the *in vitro* assays described in the specification in the rat paw oedema model are general models useful for testing anti-inflammatory activity, and are not restricted to assessment of efficacy in the treatment of arthritis. They are therefore useful as preliminary tests for efficacy in *any* inflammatory condition. (Emphasis in original)

This statement by Dr. Taylor confirms Applicants' position that the models provided in the specification support the enablement of the claimed compounds for treating inflammatory arthritis. Further discussion of the predictive value of the models used in the specification is discussed by Dr. Taylor in paragraphs 12-13 (pages 3-4) in which he describes why the antigen induced arthritis models are physiologically relevant based on similarities between pathologies associated in the model with the actual disease conditions. Dr. Taylor also points to the literature which demonstrates that the antigen induced arthritis model is a well-established experimental model of arthritis as well as other anti-inflammatory and immune based therapies (see paragraph 14 on page 4 of the Declaration). He refers to these articles as Exhibits SMT-3, SMT-4 and SMT-5.

On page 5, paragraph 16, Dr. Taylor states

> I therefore believe that a person of ordinary skill in the art would, once in possession of the present specification, have a

> reasonable expectation that the compounds of the invention would be useful and the treatment of numerous inflammatory conditions, especially several inflammatory arthritis, and most notably rheumatoid arthritides.

Dr. Taylor also provides data which are attached to the Declaration as Exhibit SMT-6. The data demonstrated that:

> antigen induced arthritis as being an established model of RA that involves stimulation of T-lymphocyte reactivity against the immunizing antigen. This model is induced by the immunization of animals with a protein antigen (methylated bovine serum albumin, ovalbumin or fibrin) and an adjuvant, followed by the intra-articular injection of the same antigen. This results in an immune-complex mediated inflammatory response, characterized by chronic synovitis, which is localized through the injected joint. (See paragraph 19 on page 5 of Dr. Taylor's Declaration).

Further evidence that the rat carrageenan-induced acute model of inflammation is useful for testing and assessing anti-inflammatory activity is provided as Exhibit SMT-7 of Dr. Taylor's Declaration. Exhibit SMT-7 is a copy of the U.S. Food and Drug Administrations Center for Biologics Evaluation Research and Guidance for Industry on "Clinical Development Programs for Drugs, Devices and Biological Products for the Treatment of Rheumatoid Arthritis (RA)." In particular, the Examiner's attention is drawn to paragraph 20 (page 6) of the Declaration wherein Dr. Taylor summarizes these guidelines in relation to the disclosure of the present specification:

> the rat carrageenan-induced acute model of inflammation is stated to be useful in assessing anti-inflammatory activity, and it is also stated that most of the animal models which involve inflammation in the paw may be used for measuring antiphlogistic (i.e., anti-inflammatory) action of a drug. This is the carrageenan-induced footpad inflammation model which is described in the present specification.

As further evidence that this model is predicative of rheumatoid arthritis and anti-inflammatories, in general, Dr. Taylor notes in paragraph 21 (page 6) that there are hundreds

of publications using the carrageenan-induced arthritis model for testing anti-inflammatory compounds.

In view of this extensive discussion of the knowledge in the field and the data of record in this application, Dr. Taylor, in paragraph 24 (page 7) concludes:

> I therefore consider that a person of ordinary skill in the art would, once in possession of the present specification, have a reasonable expectation that the compounds of the invention would be useful in the treatment of numerous inflammatory conditions, especially several inflammatory arthritis, and most notably rheumatoid arthritis. Moreover, such a person would readily be able to test efficacy of the compounds of the invention for this purpose in well-established experimental models, without the need to exercise any further inventive effort. Accordingly, I consider that the specification provides an enabling disclosure of a method of treating inflammatory arthritis, comprising the step of administering an effective amount of a compound of the invention to a mammal in need thereof.

Turning to the Declaration of Dr. Santer, it is noted that Dr. Santer also has an extensive history and knowledge in the field of connective tissue and arthritis research which is supported by the copy of her *curriculum vitae* attached to her Declaration as Exhibit VBS-1. In particular, the Examiner's attention is drawn to paragraphs 11, 12, and 13 (pages 3-4) of Dr. Santer's statements in which she confirms that

> the carrageenan-induced footpad oedema is a widely used standard assay for assessing the anti-inflammatory activity of candidate drugs for this indication, and that adjuvant-induced arthritis is also widely used for this purpose. . . For example, the rat footpad model was used for the initial demonstration of the anti-inflammatory activity of indomethacinn piroxicam, to well-known non-steroidal anti-inflammatory drugs (NSAIDs) which are very commonly used in the treatment of rheumatoid arthritis and other inflammatory arthritises, such as psoriatic arthritis and ankylosing spondylitis.

Information sheets for the NSAIDs are attached to Dr. Santer's Declaration as Exhibit VBS-4.

Based on Dr. Santer's extensive background and knowledge of the field, she concludes

> I therefore consider that long before the priority date, the experimental models described in the specification in respect of the present application were widely known in the art, and regarded as reasonably predictive of results in humans.

In view of (1) the above discussion, (2) the description in the specification, (3) the data of record in this application, (4) the Declaration of Dr. Taylor and supporting Exhibits, and (5) the Declaration of Dr. Santer and supporting Exhibits, the methods claimed in Claims 62-73 are unquestionably enabled by the specification as originally filed. Therefore, Applicants respectfully request withdrawal of this ground of rejection.

Upon withdrawal of this rejection, Applicants also request that this application be allowed. Early notice of such allowance is requested.

Respectfully submitted,

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